1631 #

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION

Group Art: 1631
Examiner: M. ALLEN
Atty. Dkt. P 0241801 (M#) | (Client Ref)

Inventor(s): LEE
Appln. No.: 08 (Series Code ↑) | 971,338 (Serial No. ↑)
Filed: November 17, 1997
Appln. Title: GDF-1 PROTEIN

OIPE APR 03 2001 PATENT & TRADEMARK OFFICE

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Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Date: April 3, 2001

AMENDMENT

This is a reply/amendment/letter in the above-identified application and includes the herewith attachment of same date and subject which is incorporated hereinto by reference and the signature below is treated as the signature to the attachment in absence of a signature thereto.

FEE REQUIREMENTS FOR CLAIMS AS AMENDED

1. Small Entity claim
A. ☐ NOT made
B. ☐ Withdrawn
C. ☐ made herewith
D. ☒ made previously
For B & C See Required Separate Paper (Pat-256)

	Claims remaining after amendment	Highest number previously paid for		Present Extra	Large/Small Entity	Additional Fee	Fee Code Lg/Sm
2. Total Effective Claims	19	**minus	20	0	x $18/$9 =	+ $0	103/203
3. Independent Claims	3	***minus	3	0	x $80/$40 =	+ $0	102/202
4. If amendment enters proper multiple dependent claim(s) into this application for first time (leave blank if this is a reissue application) ..... add					+ $270/$135 =	+ $0	104/204
5. Original due Date: January 3, 2001	☐ NONE						
6. Petition is hereby made to extend the original due date to cover the date this response is filed for which the requisite fee is attached (1 mo) (2 mos) (3 mos) (Usable only for ≤ 2mo.OA - - - 4 mos) (Usable only for 30 day/1mo.OA - - - 5 mos)				$110/$55 = $390/$195 = $890/$445 = $1390/$695= $1890/$945=	+ $445		115/215 116/216 117/217 118/218 128/228
7. Enter any previous extension fee paid since above original due date and subtract					- $0		
8. Extension Fee Attached						+ $445	
9. If Terminal Disclaimer attached, add Rule 20(d) official fee					+ $110/$55	+ $0	148/248
10. If IDS attached requires Official Fee under Rule 97 (c), ... add or if Rule 97(d) Request ..... add					+ $180 + $180	+ $0	126 126
11. After-Final Request Fee per rules 129(a) and 17(r)					+ $710/355	+ $0	146/246
12. No. of additional inventions for examination per Rule 129(b).....					x $710/355 ea	+ $0	149/249
13. Request for Continued Examination (RCE)					+ $710/355	+ $0	1179/1279
14. Petition fee for						+ $0	
15. TOTAL FEE ENCLOSED =						$445	

16. *If the entry in this space is less than entry in next space, the "Present Extra" result is "0".
17. **If the "Highest number previously paid for" in this space is less than 20, write "20" in this space.
18. ***If the "Highest number previously paid for" in this space is less than 3, write "3" in this space.

Our Deposit Account No. 03-3975)
(Our Order No. 020055 (C#) | 0241801 (M#))

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficiencies only) now or hereafter relative to this application and the resulting Official Document under Rule 20, or credit any overpayment, to our Accounting/Order Nos. shown above, for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal sheet is filed.

Query: Is appeal deadline now? If so, file Notice of Appeals separately.

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NOTE: File this cover sheet in duplicate with PTO receipt (PAT-103A) and attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LEE

Appln. No. 08/971,338

Filed: November 17, 1997

FOR: GDF-1 PROTEIN

Group Art Unit: 1631

Examiner: M.P. Allen

#17
Plunkett
4/12/01

* * * *

April 3, 2001

REPLY UNDER 37 CFR § 1.111

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the pending Office Action of October 3, 2000 (Paper No. 16), entry and consideration of the following remarks are respectfully requested.

Reconsideration and allowance are respectfully requested.

Claims 4-10 and 22-33 are pending.

35 U.S.C. § 101 – Utility

Adequate proof of any pharmacological activity constitutes a showing of practical utility. *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985). Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. *Nelson v. Bowler*, 206 USPQ 881, 883 (C.C.P.A. 1980). Because it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, adequate proof of any such activity constitutes a showing of practical utility. *Id.*

Only after the Patent Office provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Even if one of skill in the art would have reasonably questioned the asserted utility, declaration evidence alone, which shows that compounds within the scope of the

invention exhibited the asserted utility, is sufficient to satisfy the burden shifted to the applicant. *Id.* at 1441-42.

Claims 4-10 and 22-33 were rejected under Section 101 because the invention allegedly "lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility." Applicant traverses.

The Utility Examination Guidelines were published on January 5, 2001 after the mailing of this Office Action:

> [A] patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit. If an application fails to disclose one specific, substantial, and credible utility, and the examiner discerns no well-established utility, the examiner will reject the claim under section 101. The rejection shifts the burden to the applicant to show that the examiner erred, or that a well-established utility would have been readily apparent to one of skill in the art. The applicant cannot rebut the rejection by relying on a utility that would not have been readily apparent at the time the application was filed.
>
> 66 FR 1092, 1095.

Applicant submits that there are at least three utilities for GDF-1 that support the claimed invention, any one of which would be adequate to provide a practical utility. First, GDF-1 may be used as a specific marker for a tumor arising from a cell type that normally expresses the gene or protein. Second, GDF-1 may be used as a marker for a particular cell lineage. Third, GDF-1 may be used as a cell survival molecule in a neuronal culture.

With respect to the use of GDF-1 protein to make an antibody specific for the antigen, such use is well established and dependent on the utility of GDF-1 as a tumor or cell lineage marker. This is a specific utility because although any protein may be used as an antigen to raise specific antibody as stated on page 5 of Paper No. 16, GDF-1 specific antibody can be used to detect expression of GDF-1 protein like a GDF-1 probe can be used to detect expression of GDF-1 transcript. It is also substantial and credible for the reasons discussed below for tumor and cell lineage markers.

Use of GDF-1 as a tumor marker is a specific, substantial, and credible utility. The specification clearly supports the use of GDF-1 as a tumor marker (i.e., "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1," page 12, lines 20-

23). The preparation of probes complementary to GDF-1 transcripts (Example 4) and antibodies directed against GDF-1 (Example 5) were described. This utility is specific because the particular cell types detected by GDF-1 probes and antibodies are not detected by tumor markers in general. For example, such tumors may derive from tissues like the nervous system which normally express GDF-1, but not other tissues like heart and lung (Figure 7). This is a substantial utility because the ability to detect and classify metastases can determine the choice of therapy and predict its success. The working examples previously cited show that this utility is credible because GDF-1 expression at the RNA or protein level can be specifically detected using the teachings of Applicant's specification.

It is well established that lineage markers for particular cell types and stages of development have practical utility. For example, at the time of the effective filing date of this application, there were active searches for molecules like GDF-1 with restricted patterns of expression during development (see abstract of Thibodeau et al., Histochem J, 21:348-356, 1989). In contrast, the Office Action does not provide any evidence that use of GDF-1 as a lineage marker is not a well-established utility that would be readily apparent to a person of skill in the art as of the effective filing date of this application.

The specification teaches what cell types normally express GDF-1 by illustrating its temporal- and tissue-specific expression in Example 4. Following are descriptions of Northern blots hybridized with a GDF-1 probe:

Figure 6 shows a 1.4 kb GDF-1 transcript was detected in embryos of 8.5 and 9.5 days gestation, but not in later stage embryos. A second RNA species of 3.0 kb appeared at day 9.5 and persisted throughout embryogenesis.

Figure 7 shows that in adult tissues, GDF-1 was expressed almost exclusively in the brain, although GDF-1 was also detected in the adrenal gland, ovary, and oviduct. Thus, restriction of GDF-1 expression to particular adult tissues would be valuable for determining the tissue of origin of a cell or specifically targeting the cell.

The specification states, "If GDF-1 possesses [an activity similar to the nerve cell survival molecule activin], as is indicated by its specific expression in the central nervous system (see below), GDF-1 will likely prove useful *in vitro* for maintaining neuronal cultures for eventual transplantation or *in vivo* for rescuing neurons follow-

ing axonal injury or in disease states leading to neuronal degeneration" (page 14, lines 2-8). GDF-1 is described in the specification as a nerve cell survival molecule. The prediction of GDF-1 function was based in its sequence similarity to other members of the TGF-β superfamily, particularly activin, and expression in the brain. This biological activity of GDF-1 is a specific, substantial, and credible utility. Potentiation of nerve cell survival is specific for neurotrophic molecules like members of the TGF-β superfamily. This function is substantial because there it addresses unmet needs such as treating neurodegenerative disease and promoting the survival of cultured nerve cells. Assuming *arguendo* that the burden has been shifted to Applicant to prove that the asserted biological activity is not incredible, the Ebendal Declaration was submitted to rebut the rejection and to show that the Examiner erred. This utility would have been readily apparent at the time the application was filed because it was taught explicitly by the specification. Only the declaration evidence supporting this utility and rebutting the rejection was obtained after the filing of this application. This utility is specific, substantial, and credible for the reasons stated above with respect to the utility of a tumor marker.

The Guidelines admit that sequence similarity can be used as a basis for predicting a function of a putatively encoded protein and rejects a *per se* rule:

> A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. . . . More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such assertion.

66 FR 1092, 1096. Thus, there is no rule against using sequence similarity to predict a biological activity or function of GDF-1.

The Ebendal Declaration shows that GDF-1 is a nerve cell survival molecule because it potentiates the effect of neurotrophin-3 (NT-3) protein on neuronal fibre outgrowth during *in vitro* culturing. Thus, this evidence supports the predicted activity of GDF-1 as a cell survival molecule for *in vitro* culturing of neurons and shows it is error for the Office Action to allege such utility is incredible because it could not be so predicted. The results show that Applicant's predicted utility is credible.

Applicant requests withdrawal of this utility rejection made under Section 101 because the claimed invention has patentable utility.

35 U.S.C. § 112 – Enablement

A disclosure of known utility of claimed compounds as being useful and used in the same manner as defined known compounds is sufficient to satisfy the how-to-use requirement of Section 112, first paragraph. *In re Bundy*, 209 USPQ 48, 51 (C.C.P.A. 1981).

Claims 4-10 and 22-33 were rejected under Section 112, first paragraph, because a person of skill in the art allegedly "would not know how to use the claimed invention." Applicant traverses because the claimed invention has patentable utility for the reasons given above. Thus, withdrawal of this enablement rejection is requested because the specification teaches a person of skill in the art how to make and use the claimed invention.

35 U.S.C. § 112 – Written Description

Claims 4-7, 22, 24-25 and 30 were rejected under Section 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicant traverses this written description rejection because (a) the disclosed species (i.e., the mouse, human, and hamster GDF-1 genes) are representative of the claimed genus (i.e., DNA segments encoding mammalian GDF-1 protein) and (b) the Examiner's emphasis on sequence is misplaced because the structural, physical, and functional properties describing the genus provide an adequate written description of that genus.

The Office Action asserts, "The species specifically disclosed are not representative of the genus because the genus is highly variant" (page 12 of Paper No. 16). No facts are cited nor is scientific reasoning provided in the Office Action to support the allegation that the genus of mammalian GDF-1 proteins is highly variant. In contrast, this specification teaches that (1) human and mouse GDF-1 sequences are more closely related to each other (Figure 13) than to the sequences of other

TGF-β superfamily members (see Figure 3) and (2) cross-hybridization of a GDF-1 probe across different mammalian species isolates a limited number of genes.

The close sequence similarity between the human and mouse GDF-1, as well as comparison to other members of the TGF-β superfamily, would allow a person of skill in the art to determine whether a new sequence is identified as GDF-1 or not by algorithms for sequence alignment (cf. Figs. 3 and 13, and descriptions of those drawings). Furthermore, the ease with which GDF-1 genes were isolated in different mammals (i.e., DNA fractionated by agarose electrophoresis and genes detected with a GDF-1 probe) is shown by the limited number of genomic DNA bands (i.e., "single predominant band" in hamster and human DNA detected with a mouse probe in Example 3) that are detected by Southern blotting under stringent conditions. The evidence of record shows that "GDF-1 is highly conserved across species" (page 22, lines 28-29, of the specification) and refutes the allegation in the Office Action that the genus is "highly variant" (page 12 of Paper No. 16).

The cases cited in the Office Action make clear that sequence is not the only way to describe a DNA invention. Instead, the "written description" can go beyond words to the DNA's structural, physical, and functional properties. The structural properties of mammalian GDF-1 are described by the mouse and human sequences disclosed in the specification, and the similarity of those sequences to each other as compared to other TGF-β superfamily members. Physical properties of mammalian GDF-1 are described by the limited number of genes detected with a GDF-1 probe under stringent hybridization conditions and conservation of the GDF-1 gene across species. Moreover, the pending claims recite that mammalian GDF-1 protein is encoded by a claimed product or produced by a claimed method. Applicant submits that it is inherent, or at least implicit, in the claims that such GDF-1 proteins have a biological activity characteristic of the genus (e.g., a nerve cell survival molecule).

Therefore, the adequacy of the written description for the claimed genus must be determined in view of the totality of the specification's teaching the structural (i.e., similarity of amino acid sequences encoded by GDF-1 genes), physical (i.e., cross-hybridization with a GDF-1 probe of a limited number of genomic DNA bands under stringent conditions), and functional (i.e., biological activity of mammalian GDF-1 protein) properties of nucleic acids encoding mammalian GDF-1 proteins. Unlike the

cases cited in the Office Action, this application is not so limited as to disclose only a single cDNA sequence while claiming an entire genus of such sequences.

Applicant requests withdrawal of the written description rejection made under Section 112, first paragraph, because this specification conveys to a person skilled in the art with reasonable clarity that the claimed invention was in Applicant's possession as of the effective filing date of this application.

U.S. Const. amend. V – Due Process

Applicant submitted two U.S. patents (i.e., US 6,008,017 and US 6,074,841) to show that inconsistent criteria are being used to deny Applicant a patent. In those two U.S. patents, the Examiner has issued claims of similar breadth to those in this application but the patents' specification fails to provide evidence of the biological function of human cardiac/tolloid-like protein and Don-1 polypeptide, respectively. These patents are relevant to ensuring that consistent criteria are utilized by the Patent Office in determining patentability. No response was made to these arguments in the Office Action.

The refusal of the Patent Office to distinguish the patents and to apply consistent criteria for determining patentability deprives Applicant of property (i.e., his patent) without due process of law.

Conclusion

Having responded to all pending objections and rejections in Paper No. 16, Applicant urges that the claims are in condition for allowance and earnestly solicits an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is needed.

Respectfully submitted,
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